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Maya Bronfeld and Izhar Bar-Gad

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Tic Disorders: What Happens in the Basal Ganglia?

Maya Bronfeld[1] and Izhar Bar-Gad[1]

Abstract

Motor tics are brief, repetitive, involuntary movements that interfere with behavior and appear in multiple neural disorders, most notably, Tourette syndrome. Converging evidence from different lines of research point to the involvement of the corticobasal ganglia system in tics, but the neural mechanism underlying motor tics is largely unknown. An animal model directly linking basal ganglia dysfunction and motor tics indicated that local disinhibition within the basal ganglia input structure, the striatum, induces the appearance of motor tics in both rats and monkeys. Recordings of neuronal activity from multiple brain regions performed in this model during the expression of motor tics showed that tics are associated with phasic changes of neuronal activity throughout the corticobasal ganglia pathway, culminating in the disinhibition of the cortex and the release of a tic. This line of research provides a mechanistic description of the underlying neurophysiology of motor tics and may supply the much needed infrastructure for methodical hypothesis-driven studies of novel clinical treatments.

Keywords

animal model, basal ganglia, Tourette syndrome, tics

Tic Disorders

Tics are rapid, repetitive, nonrhythmic, involuntary movements or vocalizations that interfere with ongoing behavior. Tics range from "simple" movements, involving only one muscle group or simple utterances of noises or sounds, to "complex" tics, which involve sequential or coordinated activation of several muscle groups or the production of complete words or phrases. Tics appear in multiple neural disorders, but they constitute the main and defining symptom of Tourette syndrome (TS). TS patients display multiple vocal and motor tics starting in early childhood, when it has been estimated to affect up to 1% of all children. Tics expression typically fluctuates during the course of the disease, which in most cases spontaneously resolves by early adulthood. However, for a subset of patients the disease persists into adulthood, generating prolonged discomfort and disability. Most TS patients (as many as 90%) suffer from other neurobehavioral comorbid conditions, most commonly obsessive-compulsive behaviors and attention-deficit/hyperactivity disorder (Freeman and others 2000). Tics are usually highly resistant to pharmacological treatment, to the point that today medications for tics are administered only in very severe cases and the treatment goal is to reduce rather than to eliminate them. Dopamine blockers (antipsychotic drugs) are the most effective medication, but their use is restricted due to severe side effects (Eddy and others 2011). Severe treatment-refractory cases may benefit from neurosurgery in which electrodes are implanted in deep brain structures to constantly apply high-frequency electrical stimulation (Hariz and Robertson 2010). It is generally accepted that tics are caused by a central neural dysfunction rather than a psychological or peripheral source, but the precise nature of the underlying neurobiological pathology is unknown. Multiple lines of evidence point to the involvement of the corticobasal ganglia (CBG) system in tic disorders, specifically in TS, but also in its common comorbid disorders. In this update, we review findings regarding the involvement of the CBG pathway in tics and present recent studies that shed light on the pathophysiology associated with tics.

The Basal Ganglia

The basal ganglia (BG) are a group of interconnected nuclei that take part in a variety of motor, cognitive, and

[1]Bar-Ilan University, Ramat-Gan, Israel

Corresponding Author:
Dr. Izhar Bar-Gad, Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan 52900, Israel
Email: izhar.bar-gad@biu.ac.il

limbic functions. The BG integrate information from multiple cortical regions, process it, and convey it back to frontal cortical regions and brainstem nuclei. The nuclei regarded as comprising the BG are the striatum (subdivided into the putamen and caudate nuclei), the subthalamic nucleus (STN), the globus pallidus external and internal segments (GPe and GPi respectively), and the substantia nigra pars compacta and pars reticulata (SNc and SNr respectively). Excitatory projections from the cortex and thalamus are sent to the striatum and the STN. The information is then sent from these input structures to the BG's output structures—the GPi and SNr—either directly or through an interlay nucleus—the GPe (Fig. 1A). The BG system is classically described as forming a feedback loop with the cortex, as its output structures send inhibitory projections to several thalamic nuclei, which in turn project to frontal cortical areas. Inputs from motor, associative, or limbic parts of the cortex are sent to and processed within spatially distinct territories of the BG nuclei, forming several functional subcircuits (Alexander and others 1986). In the motor territory, there is a further subdivision into gross somatotopic regions specifically related to movements of the legs, arms, or face (Nambu 2011). The main neurotransmitter within the BG is the inhibitory neurotransmitter GABA, as the projection neurons in the striatum, GPe, GPi, and SNr are all GABAergic. The activity of the BG is further modulated by excitatory (glutamatergic) projections from the cortex, thalamus, and STN and by dopaminergic projections from the SNc.

Most BG nuclei contain mainly projection neurons, whose activity is modulated by the integration of inputs from other BG nuclei (Fig. 1A). The striatum is a unique exception in that it contains a complex internal network that affects its output (Fig. 1B). One element in this internal network are the abundant collateral GABAergic connections between the striatal projection neurons (termed medium spiny neurons—MSNs), which mediate a relatively weak inhibition from one projection neuron to its counterparts (Jaeger and others 1994). Another prominent feature of the internal striatal network are the local interneurons, which comprise ~25% of its neuronal population in primates (Graveland and DiFiglia, 1985). The striatum contains at least three types of local GABAergic interneurons, which form multiple inhibitory synapses onto neighboring projection neurons and are able to exert strong modulation over their activity (Koos and Tepper 1999). The striatum also contains one type of cholinergic interneurons, which were recently shown to influence its projection neurons through activation of GABAergic interneurons (English and others 2012). Thus, local GABAergic transmission is a main component of the normal functioning of the striatum.

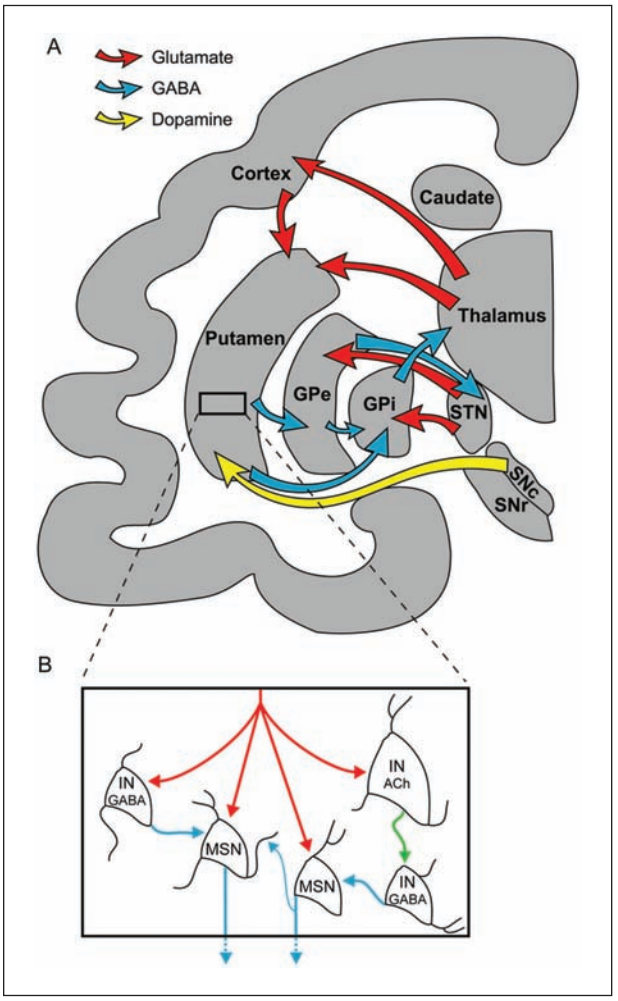

Figure 1. The corticobasal ganglia circuit. (A) Illustration of the primate brain, depicting the basal ganglia nuclei and the main connections of the corticobasal ganglia system (SNr connectivity was omitted for graphical clarity). (B) Schematic representation of the internal network of the striatum. Abbreviations: Ach = acetylcholine; GABA = gamma-aminobutyric acid; GPe = globus pallidus external segment; GPi = globus pallidus internal segment; IN = interneuron; MSN = medium spiny neuron; SNr = substantia nigra pars reticulata; SNc = substantia nigra pars compacta; STN = subthalamic nucleus.

The role of the BG in behavioral modulation remains elusive. This issue has been addresses by combining anatomical data with studies of BG activity during normal behavior and behavioral abnormalities associated with BG dysfunction. Early models described the BG as regulating the overall level of cortical excitability through changes in the tonic high-frequency inhibitory activity of the BG output structures (Albin and others 1989). An increase or a decrease in the level of activity of these structures was considered to inhibit or facilitate (disinhibit) cortical activity. The level of cortical excitability, in turn, was considered to

be positively correlated with behavior. Later models incorporated spatial and temporal properties of the BG output signal and described them as instructing the cortex which action should be selected for performance out of a multitude of potential actions (Mink 1996). According to these models, selective phasic inhibition of a group of BG output neurons accompanied by facilitation of others leads to an activation of a subset of cortical neurons encoding the selected action while inhibiting other competing actions. In such models, the extensive intrinsic inhibitory networks of the basal ganglia serve as a means of selection by which a single "winning" action reduces the activity of all others. Other models suggested a role for the BG in decorrelating cortical inputs. In these models, the BG receive and integrate many different types of information regarding the organism's state and surroundings. By their inhibitory networks, the BG compress the information and convey it in a more readily accessible form to brain regions that can use it to select and execute an optimal behavioral program (Bar-Gad and others 2003).

Evidence of BG Involvement in Tic Disorders

Converging evidence based on multiple research techniques has established a link between BG pathology and tics. Anatomical imaging studies found reductions in the volumes of the globus pallidus and striatum in TS patients (Peterson and others 2003). Moreover, the extent of volume reduction in the caudate nucleus in childhood was correlated with tic severity in later life (Bloch and others 2005). Recently, detailed postmortem anatomical studies found a reduction in the number of two types of striatal interneurons in the brains of TS patients: the GABAergic fast-spiking interneurons and the cholinergic tonically active interneurons (Kalanithi and others 2005; Kataoka and others 2010). Neurochemical imaging studies that focused on the dopaminergic system have indicated that TS is associated with increased striatal dopaminergic innervation (Albin and others 2003). Functional imaging studies found that tic expression, as well as voluntary tic suppression, were correlated with activity within the CBG (Peterson and others 1998; Wang and others 2011). Recently, the association between tics and the BG was further supported by reports of surgical interventions for tic reduction targeting these nuclei. Initial reports indicate that deep brain high frequency stimulation within the GPi or thalamus can decrease tic severity (and possibly some of the comorbid symptoms) (Hariz and Robertson, 2010).

A direct causal link between BG dysfunction and motor tics has been demonstrated in animal models of the disorder. Early studies in both rats (McKenzie and Viik, 1975; Tarsy and others 1978) and monkeys (Crossman and others 1988) showed that local disinhibition of the striatum of awake, behaving animals can induce the appearance of abnormal movements resembling motor tics. In these studies, disinhibition was achieved by local microinjections of a $GABA_A$ antagonist (picrotoxin or bicuculline) into the sensorimotor territory of the striatum. The induced abnormal movements consisted of brief, repetitive, jerk-like movements that appeared in isolated muscle groups (mostly forelimb, hindlimb, or orofacial muscles) at the contralateral side to the injected hemisphere (Fig. 2). Notably, a similar disinhibition protocol targeting other functional territories within the BG (associative or limbic) induced behavioral symptoms similar to the known comorbidities of TS (i.e., hyperactive or repetitive/compulsive behaviors) (Grabli and others 2004; Worbe and others 2009). A recent study (Gittis and others 2011) indicated that a more selective inhibition of a subpopulation of striatal GABAergic interneurons which show deficits in TS patients (Kalanithi and others 2005) could also induce motor abnormalities in mice, resembling motor tics.

Tic-Related Basal Ganglia Neurophysiology

The striatal disinhibition tic model using $GABA_A$ antagonists in animals enables a direct and detailed exploration of the patterns of abnormal neuronal activity associated with these abnormal movements. These studies have focused on neuronal activity within the different parts of the CBG pathway and the interactions between them.

Cortex and thalamus. Early recordings in rats showed that motor tics were associated with large transient deflections in the cortical electroencephalogram (EEG) activity (EEG spikes) recorded from the ipsilateral side to the disinhibited striatum (contralateral to the motor tics). The EEG spikes appeared before motor tics could be detected by electromyogram (EMG) activity, but once initiated, the tics appeared synchronously with cortical EEG spikes that continued throughout the duration of the motor effect (Tarsy and others 1978; Muramatsu and others 1990). The maximal size of the EEG spikes was recorded over the sensorimotor cortices with small EEG fluctuations over nonmotor areas (Muramatsu and others 1990). Recent recordings of individual neurons in monkeys revealed that tics were associated with a brief burst of activation of neurons in the motor cortex (McCairn and others 2009) (Fig. 3A). Tic-related cortical activations were detected both before and after the EMG-derived tic-onset time, mostly up to ±50 ms around tic onset (Bronfeld and others 2011). Notably, a similar pattern of tic-related neuronal activations was observed in the ventromedial nucleus of the rat thalamus, a structure that receives BG inputs and projects to the motor cortex (Muramatsu and others 1990) (Fig. 3B).

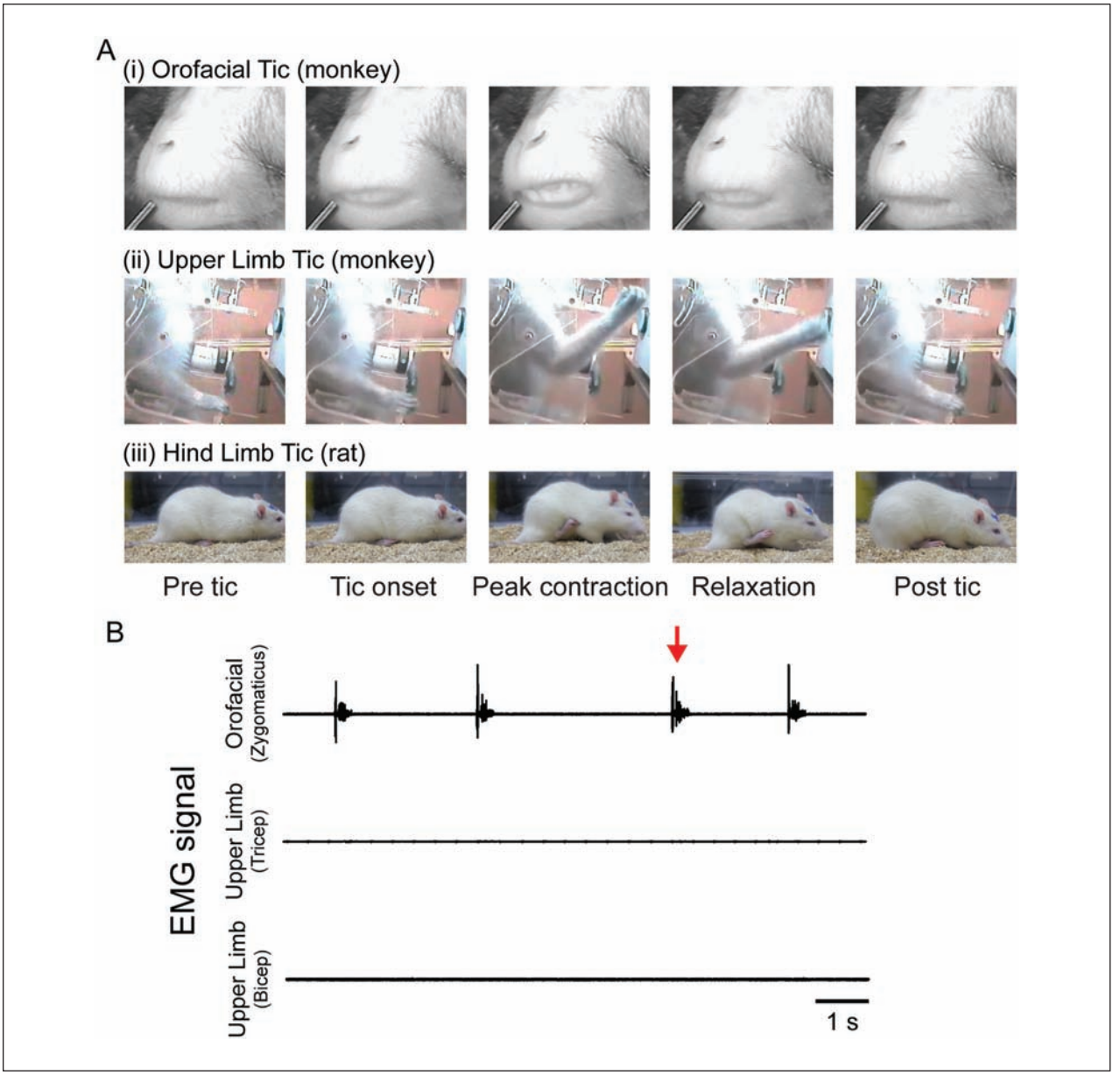

Figure 2. Tic expression in animal model of motor tics. Video and EMG recordings of motor tics induced by local microinjections of a $GABA_A$ antagonist into the striatum of the monkey and rat. (A) A sequence of frames taken from video recordings depicting the progress of a motor tic expressed in different muscles: (i) orofacial (ii) upper limb and (iii) hind limb. (B) Simultaneous EMG recordings from three muscles during the expression of orofacial motor tics in a monkey, depicting the localized nature of the tics confined to just one muscle. Red arrow indicates the timing of the tic presented in A(i).

Striatum. Recordings of neuronal activity in the striatum have focused on the activity of the projection neurons (MSNs). MSNs typically display a low-frequency bursting firing pattern (Wilson and Groves, 1981). Following administration of a $GABA_A$ antagonist in monkeys, MSNs were found to increase their overall firing rate, which could be attributed to an increase in the number of bursts and in the number of spikes within bursts (Worbe and others 2009). Analysis of MSNs activity in relation to the expression of motor tics revealed that the MSNs response to tics was a burst of activation (Fig. 3A) often preceding both the motor tic and the tic-related activation of simultaneously recorded cortical neurons (Bronfeld and others 2011). The MSNs displaying tic-related activity were unevenly distributed within the striatum. Only neurons recorded from the somatotopic striatal region

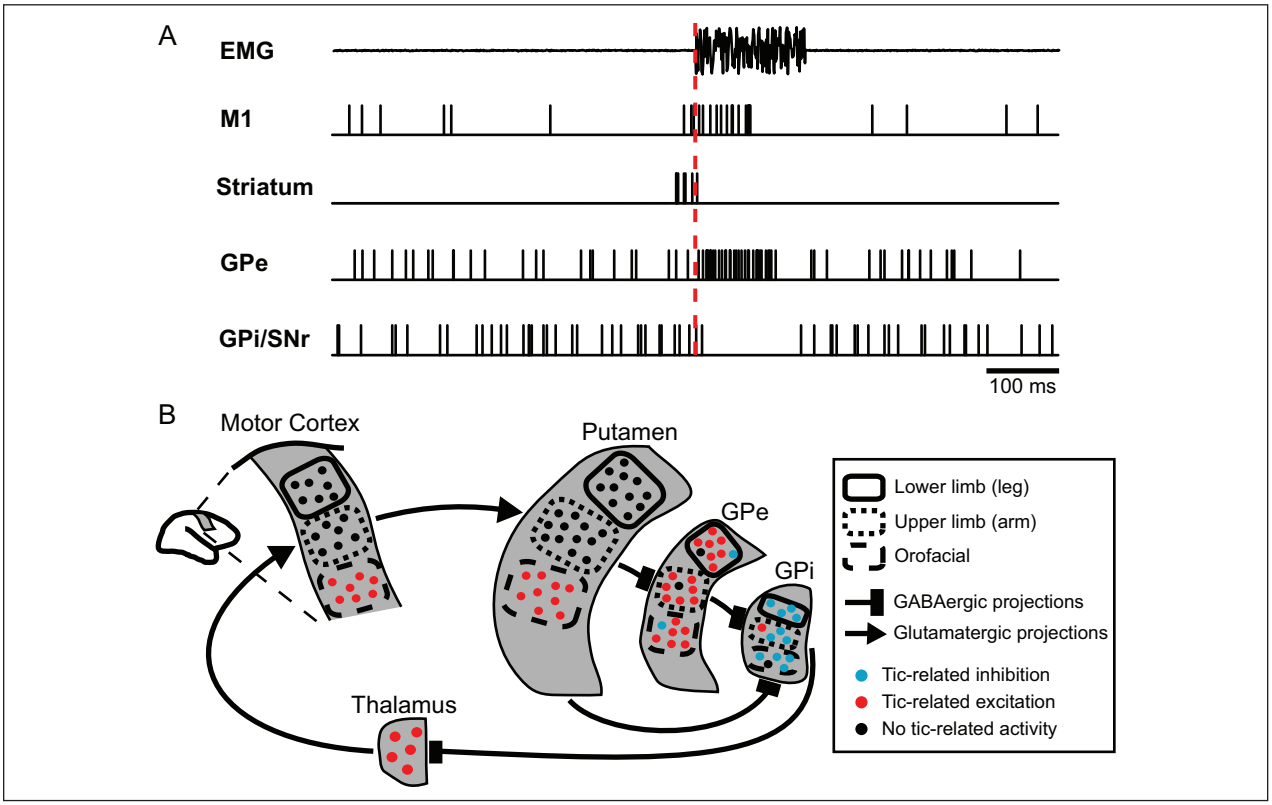

Figure 3. Tic-related neuronal activity in the CBG. (A) Simulated spike trains illustrating the main types of tic-related activity observed in the different CBG nuclei following local striatal disinhibition. Tics were associated with bursts of activity in the primary motor cortex (M1) and the striatum, phasic increases in the firing rate of most GPe neurons, and phasic decreases of firing rate in the BG output structures (GPi/SNr). (B) Schematic illustration depicting the patterns and spatial distribution of neuronal tic-related activity in the different somatotopic territories of the CBG system during the expression of focal orofacial motor tics.

associated with the body part in which motor tics appeared displayed tic-related activations, whereas neurons recorded from other parts of the striatum showed no tic-related responses (Bronfeld and others 2011) (Fig. 3B). What distinguished the MSNs tic-related activity from their normal activity was its apparent lack of specificity. In the normal state, MSNs are highly selective to different kinematic and contextual parameters of movements, such that only a subset of neurons displays phasic activations in response to any given movement. The large fraction of MSNs showing similar responses to the brief stereotypic tic movements suggests that tics may be associated with altered specificity of the MSNs (Bronfeld and Bar-Gad, 2011).

Phasic tic-related activity has also been described in another population of striatal neurons: the cholinergic interneurons (Bronfeld and others 2011). These neurons are considered to be part of the reward system, and their phasic event-related activity was shown to be modulated by dopaminergic inputs (Graybiel and others 1994). The tic-related activity observed in the cholinergic interneurons suggests that tics may be accompanied by an activation of the dopaminergic system, which is suggestive of the potential involvement of learning mechanisms in the expression of motor tics.

GPe. Neurons in both pallidal segments typically fire continuously and irregularly at high frequencies (50-80 spikes/s) and, similar to MSNs, show highly specific movement-related activity modulations. Both phasic firing rate increases and decreases are observed in pallidal neurons in response to preferred movements, with increases more frequently observed (Brotchie and others 1991). A similar pattern of phasic rate modulations (predominantly excitations) was observed in response to experimentally induced motor tics in monkeys (Fig. 3A), but tic-related activity differed from responses to normal movements in several respects. Tic-related GPe activations were of larger amplitude and observed in a larger fraction of neurons (over 70% of recorded neurons) compared with reported responses to normal movements. Furthermore, tic-related neurons were diffusely and randomly distributed within the GPe (Fig. 3B), regardless of

the locations of striatal disinhibition or the tics (Bronfeld and others 2011), supporting the concept of altered specificity in these neurons as well. The onset of GPe tic-related neuronal activity was almost always later than tic-related cortical activity and followed the onset of the tics.

BG output structures (GPi/SNr). In the normal state the patterns of GPi/SNr movement-related activity are very similar to those of the GPe (i.e., specific responses, predominantly phasic rate increases). This pattern is significantly altered during the expression of motor tics. In the animal model of motor tics, a very large fraction of recorded GPi/SNr neurons display significant tic-related activity (over 70% of recorded neurons), the majority of which display firing rate decreases, often manifesting as a complete brief cessation of firing (Muramatsu and others 1990; McCairn and others 2009) (Fig. 3A). Similar to the spatial and temporal patterns of GPe tic-related activity, tic-related GPi/SNr neurons were randomly and widely distributed (Fig. 3B) and the tic-related activity occurred at the same time or later than the tic-related cortical and striatal activations and following the onset of the tics (Muramatsu and others 1990;Bronfeld and others 2011). Notably, recordings of GPi neurons of TS patients undergoing neurosurgery found similar patterns of tic-related activity to those observed in the animal model. However, in human patients the researchers observed a subset of GPi neurons displaying very early tic-related activity (as early as 2 s before tic onset), which they suggested could be related to premonitory sensations or urges that often precede a tic in TS patients (Zhuang and others 2009).

Basal Ganglia Disinhibition as a Mechanism of Tic Formation

Inhibitory circuits are a major component of the CBG neural pathway, and animal models have demonstrated that the disruption of inhibitory (GABAergic) transmission within the BG can directly induce motor and behavioral deficits. In the motor territory of the striatum, local blockade of GABA inhibition induced motor tics that were associated with abnormal patterns of activation throughout the CBG (McCairn and others 2009; Bronfeld and others 2011). In the striatum, tics were associated with a strong activation of many of the projection neurons, suggesting a reduced specificity of the neuronal encoding. This pattern was amplified downstream in neurons of the BG output structures, which displayed widespread phasic inhibitions synchronous with the tics. Finally, the phasic removal of BG inhibition was observed in the thalamus and motor cortex, leading to tic-related neuronal activations. Motor cortex activity often preceded tic-onset and presumably encoded the tic-related muscular activation.

The relation between disrupted BG inhibition and motor tics is further supported by findings in human studies. The reduction in striatal volume and the selective loss of striatal inhibitory interneurons observed in TS patients suggests that reduced striatal inhibition plays a key role in the natural course of the disease. This hypothesis has been supported by evidence for altered cortical inhibition in TS patients that suggests a reduction of inhibitory subcortical inputs from the BG (Heise and others 2010). Abnormal disinhibition and loss of neuronal specificity are also key components of theoretical models of BG dysfunction. The loss of inhibition within the striatum leads to inappropriate activation of MSNs which should otherwise be suppressed. This joint activation of neurons may lead to the expression of abnormal movements (i.e., tics) either due to a degradation of the information conveyed to the cortex (Bar-Gad and others 2003) or direct activation of cortical neurons encoding the tic motor pattern (Mink, 2001).

Conclusions

Despite more than a century of abundant medical and scientific study, surprisingly little is known about the pathophysiology of motor tics, their underlying causes or effective treatment. The local disinhibition animal model of motor tics provides robust opportunities for a detailed exploration of the neural mechanisms involved in the generation and expression of motor tics. It is unique, in that most other animal models of TS reported thus far (genetic or pharmacological) have addressed related symptoms or pathologies of the disorder but have mostly failed to induce clear repetitive tic-like movements (Swerdlow and Sutherland 2005). Initial findings using this model suggest that disruption of the local inhibitory circuits in the motor domain of the BG is a key element of the neural mechanism underlying motor tics, and that tics are associated with a phasic and distributed (widespread) release of thalamic/cortical neurons from BG inhibitory control. Moreover, similar disinhibition in the associative and limbic domains of the BG leads to behavioral abnormalities comparable to some of the comorbid symptoms of TS. This transition from the phenomenological description provided by Gilles de la Tourette to a mechanistic description of the underlying neurophysiology may provide the much needed infrastructure for methodical hypothesis-driven studies of the causes and novel clinical treatments of the disorder.

Declaration of Conflicting Interests

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